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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	Steven Walkley
SERIAL NO.	:	10/619,378
FILED	:	July 14, 2003
FOR	:	THERAPEUTIC COMPOSITIONS AND METHODS OF TREATING GLYCOLIPID STORAGE RELATED DISORDERS

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Carolyn Di Meglio 2/13/06
(Signature and Date)

PETITION FOR GRANT OF PRIORITY UNDER 35 USC 119

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Dear Sir:

Applicant hereby petitions for grant of priority of the present Application on the basis of the following prior filed foreign Application:

COUNTRY	SERIAL NO.	FILING DATE
GREAT BRITAIN	**0100889.5**	**JANUARY 12, 2001**

To perfect Applicant's claim to priority, a certified copy of the above listed prior filed Application is enclosed.

Acknowledgment of Applicant's perfection of claim to priority is accordingly requested.

Respectfully submitted,

Sarah J. Fashena

Sarah J. Fashena, Ph.D.
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Date: February 13, 2006

The Patent Office

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

CERTIFIED COPY OF PRIORITY DOCUMENT

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

accordance with the Patents (Companies Re-registration) Rules 1982, if a company named this certificate and any accompanying documents has re-registered under the Companies Act 80 with the same name as that with which it was registered immediately before re-stration save for the substitution as, or inclusion as, the last part of the name of the words "lic limited company" or their equivalents in Welsh, references to the name of the company in s certificate and any accompanying documents shall be treated as references to the name vi which it is so re-registered.

ac dance with the rules, the words "public limited company" may be replaced by p.l.c., P C. or PLC.

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Dated 27 January 2006

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THE PATENT OFFICE
A
12 JAN 2001
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Request for grant of a patent

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The Patent Office

Cardiff Road
Newport
South Wales
NP9 1RH

1. Your reference PWC/P21712GB

2. Patent application number *(The Patent Office will fill in this part)* **0100889.5** 12 JAN 2001

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

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86 Milton Park
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Patents ADP number *(if you know it)* 7112386002

If the applicant is a corporate body, give the country/state of its incorporation: England

4. Title of the invention

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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5/1/06
24/1/06

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Forrester House
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London N11 2EY

Patents ADP number *(if you know it)* 125001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

Patents Form 1/77

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Description	21
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Abstract	-
Drawing *(s)*	2 + 2

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Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 12/01/2001

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr Paul W. Chapman
Tel: 020 7539 4200

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COMPOUNDS

The present invention relates to novel compounds useful as inhibitors of glucosylceramide synthase (GCS; UDP-glucose:ceramide glycosyltransferase UDP-glucose:*N*-acylsphingosine D-glucosyltransferase, EC 2.4.1.80). The compounds find use in the treatment of glycolipid storage diseases, diseases associated with glycolipid accumulation, cancers in which glycolipid synthesis is abnormal, infectious diseases caused by organisms which use cell surface glycolipid as receptors, infectious diseases in which synthesis of glucosylceramide is essential or important, diseases in which excessive glycolipid synthesis occurs, neuronal disorders and neuronal injury. Their synthesis is also described, as are pharmaceutical formulations comprising the compounds and methods of treatment using the compounds.

GCS is an intracellular enzyme that catalyzes the assembly of uridine diphosphate-glucose and ceramide into the glycolipid, glucosylceramide . GCS's role in biology is currently the subject of intense basic and applied science interest. For example, many investigators are exploring the role of GCS in regulating ceramide levels since this molecule can induce apoptotic cell death (*J Biol Chem* 2000 Mar 10;275(10):7138-43). Similarly, there is active research into the role of GCS in maintaining cholesterol/glycolipid 'rafts,' cell-surface membrane domains of specialized permeability and functionality that appear to be involved in a variety of signal transduction events (Nature. 1997 Jun 5;387(6633):569-72.).

GCS also is a target for treating certain human diseases. Glucosylceramide and structurally related glycolipids are stored in the lysosomes of patients with genetic diseases which result from a mutation in one of the essential glycolipid-degrading enzymes (*e.g.*, Gaucher, Tay Sachs, Sandhoffs, GM1 gangliosidosis and Fabry diseases). Glycolipid storage also occurs as a secondary effect in some tissues (*e.g.*, neuronal tissue) with genetic storage diseases such as Niemann-Pick C disease, mucopolysaccharidoses, mucolipidosis type IV (Proc Natl Acad Sci U S A. 1998 May 26;95(11):6373-8) and α-mannosidosis (Proc Natl Acad Sci U S A. 1991 Dec 15;88(24):11330-4). It has been reasoned that GCS inhibitors may be applied to reduce the rate of glycolipid synthesis in diseased cells so that there is less glycolipid present to be stored, a treatment approach termed substrate deprivation. Studies have

demonstrated that GCS inhibitors can in fact be used to reduce the glycolipid accumulation seen in cell and animal models of glycolipid storage (Proc Natl Acad Sci U S A. 1999 May 25;96(11):6388-93; Science. 1997 Apr 18;276(5311):428-31; J Clin Invest. 2000 Jun;105(11):1563-71). Furthermore, a recent clinical trial report has shown that GCS inhibitors such as Vevesca (N-butyldeoxynojirimycin) are useful in treating human patients with Gaucher disease (Lancet. 2000 Apr 29;355(9214):1481-5).

The use of GCS inhibitors in the treatment of human malignancies has long been proposed. Tumours can synthesize abnormal quantities of glycolipids and/or glycolipids not present in the normal tissue. In addition glycolipids or gangliosides in particular are shed by tumour cells and released into the extracellular space and the bloodstream. Both tumour shed and cell surface bound tumour gangliosides can influence tumour host cell interactions such as cell-cell contacts or adhesion (Methods Enzymol. 2000;312:447-58.), cell motility (Mol Chem Neuropathol. 1995 Feb-Apr;24(2-3):121-35.), growth factor signalling events (J Biol Chem. 2000 Nov 3;275(44):34213-23), tumour stimulated angiogenesis (Acta Oncol. 1997;36(4):383-7) and tumour specific immune responses (J Immunol. 1999 Oct 1;163(7):3718-26). All these events can affect tumour development and progression. Glycolipids, glucosylceramide in particular, are known to accumulate in multidrug resistant (MDR) tumour cells (Anticancer Res. 1998 Jan-Feb;18(1B):475-80) and *in vitro* treatment of these cells with GCS inhibitors can reverse the MDR phenotype (J Biol Chem. 1997 Jan 17;272(3):1682-7; Br J Cancer. 1999 Oct;81(3):423-30).

Cell surface glycolipids also have roles in infectious disease, serving as receptors for the binding of pathogenic bacteria (APMIS. 1990 Dec;98(12):1053-60. Review.), fungi (Infect Immun. 1990 Jul;58(7):2085-90) and viruses (FEBS Lett. 1984 May 7;170(1):15-8). In addition, glycolipids on the surface of cells are bound by bacterial toxins (Methods Enzymol. 2000;312:459-73) for instance the B subunit of cholera toxin (ganglioside GM1) and verocytotoxin (globotriaosylceramide GB3).

The use of GCS inhibitors may also be appropriate in a number of other clinical indications which are associated with abnormalities in glycolipid synthesis. Atherosclerotic lesions of human aorta have a higher ganglioside content than

unaffected regions of the aorta and serum ganglioside concentrations in atherosclerotic patients are higher than in normal individuals (Lipids 1994 vol. 29(1):1-5). Tissue derived from the kidneys of patients with polycystic kidney disease contains high levels of both glucosylceramide and lactosylceramide (J Lipid Res. 1996 Jun;37(6):1334-44). Renal hypertrophy in an animal model of diabetes is associated with increases in glycolipid synthesis, (J Clin Invest. 1993 Mar;91(3):797-803).

Glycolipid metabolism also plays a critical role in other neuronal disorders, such as Alzheimer's disease and epilepsy. For instance, Niemann-Pick C (NPC) patient neurons present with fibrillar tangles reminiscent of the morphology seen in Alzheimer's disease.

Interestingly, GM1 ganglioside binding by amyloid beta-protein induces conformational changes that support its formation of fibrous polymers, and the fibrillar deposition of this protein is an early event in Alzheimer's disease (Yanagisawa et al (1995) Nat Med 1: 1062-6, Choo-Smith et al (1997) Biol Chem 272: 22987-90). Thus, decreasing GM1 synthesis with agents such as NB-DNJ could inhibit the fibre formation seen in Alzheimer's disease.

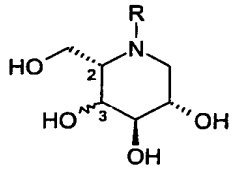
In contrast, preliminary clinical trials have shown that neurodegenerative processes seen with Parkinson's disease, stroke and spinal cord injuries seem to improve by treating patients with GM1 ganglioside (Alter (1998) Ann N YAcad Sci 845: 391-4011; Schneider (1998) Ann N YAcad Sci 845: 363-73; Geisler (1998) Ann N YAcad Sci 845: 374-81). It is possible that co-administering glucosylceramide synthesis inhibitors would provide the clinician greater control over this treatment course. Inhibitors like NB-DNJ would limit patient-specific inconsistencies by blocking their neuronal glycolipid synthesis. In addition, inhibiting glucosylceramide synthesis would limit the metabolism of administered glycolipids into other, perhaps unproductive, forms. Thus, the ability to modulate glucosylceramide synthesis with inhibitors such as NB-DNJ may be useful is treatment of a wide variety of neuronal disorders.

It has also been shown that glucosylceramide synthesis inhibitors can reversibly

induce male sterility and can therefore be used as male contraceptives.

Given the importance of GCS in a wide spectrum of basic and ~~applied science~~ interests, it is essential that new tools that provide a means for modulating this enzyme's function be developed. Towards this end, we have synthesized a number of novel compounds that are useful in inhibiting GCS's catalytic activity.

Thus, in a first aspect, the present invention provides a compound of formula I:



(I)

wherein

R is hydrogen, C_{1-16} straight or branched-chain alkyl, C_{1-10} alkylaryl where aryl is phenyl, pyridyl, thienyl or furyl wherein phenyl is optionally substituted by one or more substituents selected from F, Cl, Br, CF_3, OCF_3, OR^1, C_{1-6} straight or branched-chain alkyl; and

R^1 is hydrogen, C_{1-6} straight or branched-chain alkyl, and pharmaceutically acceptable salts thereof.

The hydroxyl group at position 3 may be fixed in either an α or β configuration relative to the other hydroxyl groups in I.

Preferred compounds of the invention include

3,4,5-Piperidinetriol, 1-propyl-2-(hydroxymethyl)-, (2S,3R,4R,5S)

3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2S,3R,4R,5S)

3,4,5-Piperidinetriol, 1-pentyl-2-(hydroxymethyl)-, (2S,3R,4R,5S)

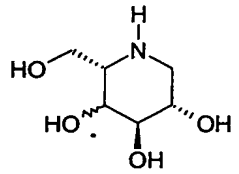
3,4,5-Piperidinetriol, 1-heptyl-2-(hydroxymethyl)-, (2S,3R,4R,5S)

3,4,5-Piperidinetriol, 1-butyl-2-hydroxymethyl)-, (2S,3S,4R,5S)

As described herein, the compounds of the present invention can be used for the inhibition of GCS. Thus, in a second aspect, the present invention provides the use of the compounds of the invention in medicine.

According to a third aspect of the invention, the compounds defined by (I) may be prepared by any suitable method known in the art and/or by processes comprising:

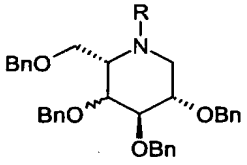
(a) reacting a compound of formula (II):



(II)

with $NaBH_3CN$ and an aldehyde of formula R^2CHO, wherein $R^2 = C_{1-15}$ straight or branched-chain alkyl, in acetic acid-methanol, or with $NaBH(OAc)_3$ and an aldehyde of formula R^2CHO, wherein $R^2 = C_{1-15}$ straight or branched-chain alkyl, in a solvent such as dichoromethane; or

(b) reacting a compound of formula (III):

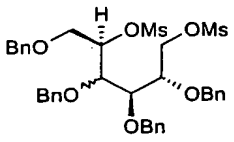


Bn = CH_2Ph

(III)

wherein R is as defined in formula (I), in the presence of hydrogen gas and a catalyst such as $PdCl_2$ or palladium on carbon in a suitable solvent such as an alcohol, eg ethanol. It will be understood that when R = CH_2Ph this group can also be removed under these conditions to give compounds of formula (II).

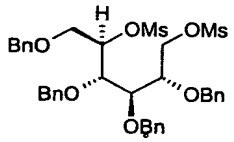
Compounds of formula (III) may be prepared by reacting a compound of formula (IV):



(IV)

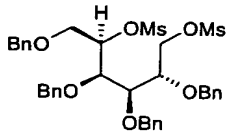
with an amine of formula RNH_2, wherein R is as defined in formula (I), either neat or in a solvent such as tetrahydofuran.

Compound (IVa) is a known compound: V.S. Rao *et al.*, *Can. J. Chem.* (1981), **59**(2), 333-8; P.A. Fowler et al., Carbohydr. Res. (1993), 246 377-81.



(IVa)

Compound (IVb) may be prepared by reacting 2,3,4,6-tetra-O-benzyl-D-galactitol with mesyl chloride in the presence of a base such as pyridine.



(IVb)

Any novel intermediate compounds as described herein also fall within the scope of the present invention.

According to a fourth aspect the present invention provides pharmaceutical formulations comprising one or more of the compounds of the invention, together with one or more pharmaceutically acceptable carriers or excipients.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per dose. Such a unit may contain for example 10mg/kg to 600mg/kg, preferably 50mg/kg to 300mg/kg and more preferably 50mg/kg to 150mg/kg depending on the condition being treated, the route of administration and the age, weight and condition of the patient.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may

be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For applications to the eye or other external tissues, for example the mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may also include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds of the present invention are useful in that they are capable of inhibiting glucosylceramide synthase. Thus, the compounds of the invention can be used in the treatment of various glycolipid storage diseases such as Gaucher's disease, Sandhoff's disease, Tay-Sachs disease, Fabry disease, GM1 gangliosidosis etc. In addition, compounds such as this also can find use in the treatment of conditions in which glycolipid accumulation occurs such as Niemann-Pick disease, mucopolysaccharidoses (MPS I, MPS IIIA, MPS IIIB, MPS VI and MPS VII), mucolipidosis type IV and α-mannosidosis.

The compounds of the present invention can also be used in the treatment of cancers in which glycolipid synthesis is abnormal such as brain tumours, neuroblastoma, malignant melanoma, renal adenocarcinoma and multi-drug resistant cancers in general.

The compounds of the present invention can also be used in the treatment of disease caused by infectious organisms which use cell surface glycolipid as receptors for the infectious organism or toxin produced by the infectious organism.

The compounds of the present invention can also be used in the treatment of disease caused by infectious organisms for which the synthesis of glucosylceramide is an essential or important process such as the pathogenic fungus *cryptococcus neoformans*. The compounds of the present invention can also be used in the treatment of disease in which excessive glycolipid synthesis occurs such as but not limited to , atherosclerosis, polycystic kidney disease and diabetic renal hypertrophy.

The compounds of the present invention can also be used in the treatment of neuronal disorders, such as Alzheimer's disease and epilepsy

The compounds of the present invention can also be used in the treatment of neuronal degenerative disease such as Parkinsons' disease

The compounds of the present invention can also be used in the treatment of neuronal injury such as spinal cord injuries or stroke.

In additional aspects, therefore, the present invention provides:

(i) the use of a compound of the invention as an inhibitor of glucosylceramide synthase;

(ii) the use of a compound of the invention in the manufacture of a medicament for the treatment of a glycolipid storage disease. Examples of glycolipid storage disease which can be treated include, but are not limited to: Gaucher disease, Sandhoffs disease, Tay-Sachs disease, Fabry disease or GM1 gangliosidosis;

(iii) the use of a compound of the invention in the manufacture of a medicament for the treatment of Niemann-Pick disease types A and C.

(iv) the use of a compound of the invention in the manufacture of a medicament for the treatment of mucopolysaccharidosis type I, mucopolysaccharidosis type IIID, mucopolysaccharidosis type IIIA, mucopolysaccharidosis type VI and mucopolysaccharidosis type VII.

(v) the use of a compound of the invention in the manufacture of a medicament for the treatment of α-mannosidosis and mucolipidosis type IV.

(vi) the use of a compound of the invention in the manufacture of a medicament for the treatment of, but not limited to neuronal cancer including neuroblastoma, brain cancer, renal adenocarcinoma, malignant melanoma, multiple myeloma and multi-drug resistant cancers.

(vii) the use of a compound of the invention in the manufacture of a medicament for use in the treatment of Alzheimer's disease, epilepsy or stroke;

(viii) the use of a compound of the invention in the manufacture of a medicament for use in the treatment of Parkinson's disease;

(ix) the use of the compound of the invention in the manufacture of a medicament in the treatment of spinal injury.

(x) the use of a compound of the invention in the manufacture of a medicament for use in the treatment of disease caused by infectious microorganisms which utilize glycolipids on the surface of cells as receptors for the organism itself or toxins produced by the organism.

(xi) the use of a compound of the invention in the manufacture of a medicament for use in the treatment of disease caused by infectious organisms for which the synthesis of glucosylceramide is an essential or important process such as but not limited to pathologies associated with infections of the pathogenic fungus *cryptococcus neoformans*.

(xii) the use of a compound of the invention in the manufacture of a medicament for use in the treatment of diseases associated with abnormal glycolipid synthesis including but not limited to polycystic kidney disease, diabetic renal hypertrophy and atherosclerosis.

(xiii) the use of a compound in the manufacture of a medicament for the treatment of a condition treatable by the administration of a ganglioside such as GM1 ganglioside. Examples of such conditions are Parkinson's disease, stroke and spinal cord injuries.

(xiv) the use of a compound of the invention in the manufacture of a medicament for reversibly rendering a male mammal infertile;

(xv) a method for the treatment of a glycolipid storage disease, eg Gaucher's disease, Sandhoff's disease, Tay-Sachs disease or GM1 gangliosidosis, which comprises the step of administering to a patient an effective amount of a compound of the invention;

(xvi) a method for the treatment of Niemann-Pick disease, which comprises the step of administering to a patient an effective amount of a compound of the invention;

(xvii) a method for the treatment of mucopolysaccharidosis type I, mucopolysaccharidosis type IIID, mucopolysaccharidosis type IIIA, mucopolysaccharidosis type VI and mucopolysaccharidosis type VII which comprises the step of administering to a patient an effective amount of a compound of the invention;

(xviii) a method for the treatment of α-mannosidosis and mucolipidosis type IV which comprises the step of administering to a patient an effective amount of a compound of the invention;

(xix) a method for the treatment of but not limited to neuronal cancer including neuroblastoma, brain cancer, renal adenocarcinoma, malignant melanoma, multiple myeloma and multi-drug resistant cancers which comprises the step of administering to a patient an effective amount of a compound of the invention;

(xx) a method for the treatment of disease caused by infectious microorganisms which utilize glycolipids on the surface of cells as receptors for the organism itself or toxins produced by the organism which comprises the step of administering to a patient an effective amount of a compound of the invention;

(xxi) a method for the treatment of disease caused by infectious organisms for which the synthesis of glucosylceramide is an essential or important process such as but not limited to pathologies associated with infections of the pathogenic fungus *cryptococcus neoformans* which comprises the step of administering to a patient an effective amount of a compound of the invention.

(xxii) a method for the treatment of diseases associated with abnormal glycolipid synthesis including but not limited to polycystic kidney disease, diabetic renal hypertrophy and atherosclerosis, which comprises the step of administering to a patient an effective amount of a compound of the invention.

(xxiii) a method for the treatment of Alzheimer's disease, epilepsy, stroke or spinal injury which comprises the step of administering to a patient an effective amount of a compound of the invention;

(xxiv) a method for the treatment of Parkinson's disease, which comprises the step of administering to a patient an effective amount of a compound of the invention.

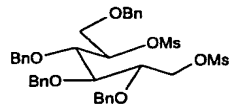
(xxv) a method for reversibly rendering a male mammal infertile, which comprises the step of administering to said male mammal an effective amount of a compound of the invention.

The invention will now be described with reference to the following examples, which should not be construed as in any way limiting the invention.

FIGURE 1: shows representative pathways for the metabolism of glycolipids in mammalian cells. The reaction catalyzed by glucosylceramide synthase, the assembly of uridine diphosphate-glucose and ceramide into glucosylceramide, is shown. Enzyme pathways resulting in the human glycolipid storage diseases, as well as the glucosylceramide synthase reaction inhibited by Vevesca (N-butyldeoxynojirimycin) are also represented. Abbreviations: UDP-Glc, uridine diphosphoglucose; Cer, ceramide; Sial, sialic acid; Gal, galactose; GalNAc, N-acetylgalactosamine; Glc, glucose; and

FIGURE 2: shows (a) a thin layer chromatography (TLC) chromatogram of the non-polar lipid fraction extracted from MCF-7 breast carcinoma cells treated for 7 days with 50μM example 7 compound (1), MCF-7 breast carcinoma cells (2) and (3) represent a glucosylceramide standard; and (b) represents a measure of the glucosylceramide band intensity from the TLC chromatogram relative to background with (1) representing example 7 compound treated sample and (2) the untreated control.

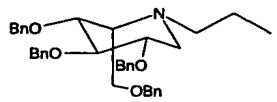
Example 1 2,3,4,6-Tetra-*O*-benzyl-1,5-di-*O*-mesyl-D-glucitol



2,3,4,6-Tetra-*O*-benzyl-D-glucitol (45g) was dissolved in pyridine (200 ml) and added over 30 minutes to a solution of mesyl chloride (15 ml) in pyridine (100 ml) at 0°C. The clear solution was stored at 4°C overnight, after which time TLC analysis showed completion of the reaction. The reaction mixture was partitioned between ethyl

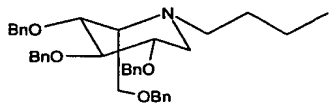
acetate and water/ice. The organic fractions were washed with 5% hydrochloric acid then saturated aqueous sodium bicarbonate solution, dried over Na_2SO_4 and concentrated to a yellow/orange oil. The oil was azeotroped with toluene and used directly in the next stage (Example 2-5).

Example 2 Piperidine, 1-propyl-3,4,5-tris(phenylmethoxy)-2-[(phenylmethoxy)methyl], (2S,3R,4R,5S)



The crude 2,3,4,6-tetra-*O*-benzyl-1,5-di-*O*-mesyl-D-glucitol (988mg) was dissolved in n-propylamine (10ml) and stirred at 55°C for 4 days. TLC analysis indicated the reaction had gone to completion. The reaction mixture was concentrated and the resultant crude oil was purified by flash chromatography (gradient elution of 0 → 16% ethyl acetate/petroleum ether) to give piperidine, 1-propyl-3,4,5-tris(phenylmethoxy)-2-[(phenylmethoxy)-methyl], (2S,3R,4R,5S) (610mg, 73%). ^1H NMR ($CDCl_3$): δ 0.9 (3H, t), 1.4 (2H, m), 2.45 (2H, m), 2.6 (1H, m), 2.8 (1H, dd, J 5, 11 Hz), 3.3 (1H, m), 3.5 (2H, m), 3.6 (2H, m), 3.7 (1H, dd), 4.4- 4.8 (8H, m, OCH_2Ph), 7.2- 7.4 (20H, m, Ar*H*).

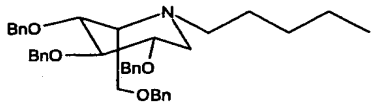
Example 3 Piperidine, 1-butyl-3,4,5-tris(phenylmethoxy)-2-[(phenylmethoxy)-methyl], (2S,3R,4R,5S)



The crude 2,3,4,6-tetra-*O*-benzyl-1,5-di-*O*-mesyl-D-glucitol (30g) was dissolved in n-butylamine (200ml) and stirred at 50°C for 4 days. TLC analysis indicated the reaction had gone to completion. The reaction mixture was concentrated and the resultant crude oil was purified by flash chromatography (gradient elution of 0 → 16% ethyl acetate/petroleum ether) to give piperidine, 1-butyl-3,4,5-tris(phenylmethoxy)-2-[(phenylmethoxy)-methyl], (2S,3R,4R,5S) (23g, 90%). ^1H NMR ($CDCl_3$): δ 0.9 (3H, t), 1.2 (2H, m), 1.4 (2H, m), 2.5 (2H, m), 2.7 (1H, m), 2.9

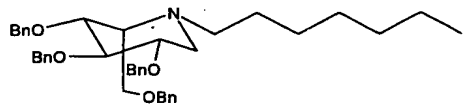
(1H, dd, J 6, 12 Hz), 3.4 (1H, m), 3.5 (1H, AB quartet J 10 Hz), 3.55 (1H, m), 3.65 (1H, m), 3.7 (1H, dd, J 2, 13 Hz), 3.8 (1H, dd, J 6, 10 Hz), 4.4- 4.9 (8H, m, O*CH*$_2$Ph), 7.2- 7.4 (20H, m, Ar*H*).

Example 4 Piperidine, 1-pentyl-3,4,5-tris(phenylmethoxy)-2-[(phenyl-methoxy)methyl], (2S,3R,4R,5S)



The crude 2,3,4,6-tetra-*O*-benzyl-1,5-di-*O*-mesyl-D-glucitol (1g) was dissolved in n-pentylamine (10ml) and stirred at 55°C for 4 days. TLC analysis indicated the reaction had gone to completion. The reaction mixture was concentrated and the resultant crude oil was purified by flash chromatography (gradient elution of 0 → 12% ethyl acetate/petroleum ether) to give piperidine, 1-pentyl-3,4,5-tris(phenylmethoxy)-2-[(phenylmethoxy)-methyl], (2S,3R,4R,5S) (680mg, 76%). ^{1}H NMR ($CDCl_3$): δ 1.0 (3H, t), 1.2 (2H, m), 1.4 (4H, m), 1.6(2H, m), 2.7 (2H, m), 2.85 (1H, m), 3.05 (1H, dd, J 5, 10.5 Hz), 3.55 (1H, m), 3.7 (2H, m), 3.85 (2H, m), 3.95 (1H, dd, J 5, 9 Hz), 4.6- 5.05 (8H, m, O*CH*$_2$Ph), 7.4- 7.5 (20H, m, Ar*H*).

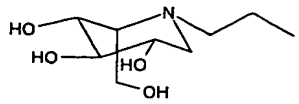
Example 5 Piperidine, 1-heptyl-3,4,5-tris(phenylmethoxy)-2-[(phenyl-methoxy)methyl], (2S,3R,4R,5S)



The crude 2,3,4,6-tetra-*O*-benzyl-1,5-di-*O*-mesyl-D-glucitol (1g) was dissolved in n-heptylamine (10ml) and stirred at 55°C for 4 days. TLC analysis indicated the reaction had gone to completion. The reaction mixture was concentrated and the resultant crude oil was purified by flash chromatography (gradient elution of 0 → 25% diethyl ether/petroleum ether) to give piperidine, 1-heptyl-3,4,5-tris(phenylmethoxy)-2-[(phenylmethoxy)-methyl], (2S,3R,4R,5S) (690mg, 76%). ^{1}H NMR ($CDCl_3$): δ 0.9 (3H, t), 1.3 (8H, m), 1.4 (2H, m), 2.5 (2H; m), 2.7 (1H, m), 2.9

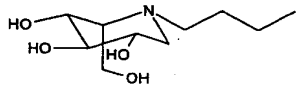
(1H, dd, J 5, 11 Hz), 3.4 (1H, m), 3.55 (2H, m), 3.7 (2H, m), 3.8 (1H, dd, J 6, 13 Hz), 4.4- 4.9 (8H, m, OCH_2Ph), 7.2- 7.4 (20H, m, Ar*H*).

Example 6 3,4,5-Piperidinetriol, 1-propyl-2-(hydroxymethyl)-, (2S,3R,4R,5S)



Piperidine, 1-propyl-3,4,5-tris(phenylmethoxy)-2-[(phenylmethoxy)-methyl], (2S,3R, 4R,5S) (610mg) was dissolved in MeOH (10ml) and stirred overnight under a hydrogen atmosphere in the presence of $PdCl_2$ (300mg). TLC indicated completion of the reaction. The reaction mixture was filtered through celite (followed by a methanol/water wash) and the filtrate concentrated. The solution was diluted with water (10ml) and slowly loaded onto 5g of Dowex 50X4-200 resin that had been pre-washed with hydrochloric acid. The resin was washed with water and then eluted with a mixture of 1:7 conc. aqueous ammonia:water. Product fractions were concentrated to give 3,4,5-piperidinetriol, 1-propyl-2-(hydroxymethyl)-, (2S,3R,4R,5S) (200mg, 90%) as a gummy solid. ^1H NMR (D_2O): δ 0.75(3H, t), 1.35(2H, m), 2.45(3H, m), 2.75(1H, dd, J = 5, 12.5Hz), 3.0(1H, dd, J = 4, 9Hz), 3.3(1H, t), 3.45(1H, m), 3.6(1H, dd, J = 5, 10Hz), 3.7(2H, m).

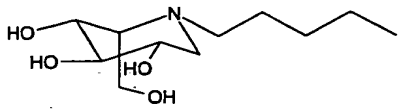
Example 7 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2S,3R,4R,5S)



Piperidine, 1-butyl-3,4,5-tris(phenylmethoxy)-2-[(phenylmethoxy)-methyl], (2S,3R, 4R,5S) (15g) was dissolved in MeOH (300ml) and stirred overnight under a hydrogen atmosphere in the presence of $PdCl_2$ (5g). TLC indicated completion of the reaction. The reaction mixture was filtered through celite (followed by a methanol/water wash) and the filtrate concentrated to ca. 50ml. The solution was slowly loaded onto 70g of Dowex 50X12-200 resin that had been pre-washed with hydrochloric acid. The resin was washed with water and then eluted with a mixture of 1:7 conc. aqueous ammonia:water. Product fractions were concentrated to give 3,4,5-piperidinetriol, 1-

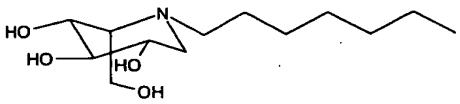
butyl-2-(hydroxymethyl)-, (2S,3R,4R,5S) (4.8g, 85%) as a colourless oil. ^{1}H NMR (D_2O): δ 0.90(3H, t), 1.31(2H, m), 1.49(2H, m), 2.53(1H, dd), 2.63(1H, ddd), 2.72(1H, ddd), 2.87(1H, dd), 3.14(1H, q), 3.44(1H, t), 3.61(1H, ddd), 3.75(1H, dd), 3.85(1H, dd), 3.89(1H, dd).

Example 8 3,4,5-Piperidinetriol, 1-pentyl-2-(hydroxymethyl)-, (2S,3R,4R,5S)



Piperidine, 1-pentyl-3,4,5-tris(phenylmethoxy)-2-[(phenylmethoxy)-methyl], (2S,3R, 4R,5S) (680mg) was dissolved in MeOH (10ml) and stirred overnight under a hydrogen atmosphere in the presence of $PdCl_2$ (300mg). TLC indicated completion of the reaction. The reaction mixture was filtered through celite (followed by a methanol/water wash) and the filtrate concentrated. The concentrate was diluted with water and slowly loaded onto 5g of Dowex 50X4-200 resin that had been pre-washed with hydrochloric acid. The resin was washed with water and then eluted with a mixture of 1:7 conc. aqueous ammonia:water. Product fractions were concentrated to give 3,4,5-piperidinetriol, 1-pentyl-2-(hydroxymethyl)-, (2S,3R,4R,5S) (240mg, 90%) as a gummy solid. ^{1}H NMR (D_2O): δ 0.75(3H, t), 1.15(4H, m), 1.35(2H, m), 2.35(1H, dd, J = 10, 12.5Hz), 2.5(2H, m), 2.7 (1H, dd, J = 5, 12Hz), 3.0(1H, dd, J = 4, 9Hz), 3.25(1H, t), 3.45(1H, m), 3.6(1H, dd, J = 5, 10Hz), 3.75(2H, m).

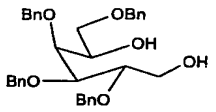
Example 9 3,4,5-Piperidinetriol, 1-heptyl-2-(hydroxymethyl)-, (2S,3R,4R,5S)



Piperidine, 1-heptyl-3,4,5-tris(phenylmethoxy)-2-[(phenylmethoxy)-methyl], (2S,3R, 4R,5S) (690mg) was dissolved in MeOH (10ml) and stirred overnight under a hydrogen atmosphere in the presence of $PdCl_2$ (350mg). TLC indicated completion of the reaction. The reaction mixture was filtered through celite (followed by a methanol/water wash) and the filtrate concentrated. The concentrate was diluted with

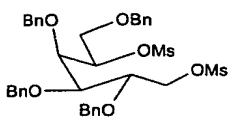
water (5ml) and slowly loaded onto 5g of Dowex 50X4-200 resin that had been pre-washed with hydrochloric acid. The resin was washed with water and then eluted with a mixture of 1:7 conc. aqueous ammonia:water. Product fractions were concentrated to give 3,4,5-piperidinetriol, 1-heptyl-2-(hydroxymethyl)-, (2S,3R,4R,5S) (260mg, 90%) as a gummy solid. ^{1}H NMR (D_2O): δ 0.7(3H, t), 1.1(8H, m), 1.3(2H, m), 2.45(3H, m), 2.7(1H, dd, J = 5, 10Hz), 2.95(1H, dd, J = 4, 9Hz), 3.25(1H, t), 3.4(1H, m), 3.55(1H, dd, J = 5.5, 9.5Hz), 3.65(2H, m).

Example 10 2,3,4,6-Tetra-*O*-benzyl-D-galactitol



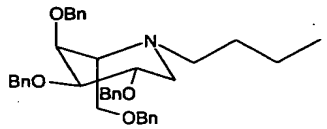
2,3,4,6-Tetra-*O*-benzyl-D-galactopyranose (107g) was dissolved in ethanol (0.6L) and, whilst stirring at 0°C, sodium borohydride (31g) was added. After stirring overnight TLC analysis indicated completion of the reaction. The ethanol solution was partitioned between water (3L) and ether (1.5L). The organic phase was dried over sodium sulfate, filtered and concentrated. The resulting oil was purified by flash chromatography (gradient elution using 20→50% ethyl acetate/petroleum ether) and then crystallised from a mixture of ethyl acetate/petroleum ether to give 2,3,4,6-tetra-*O*-benzyl-D-galactitol (97g, 91%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.4 (1H, bs), 3.35 (1H, bs), 3.55 (2H, m), 3.8 (3H, m), 3.9 (2H, m), 4.1 (1H, m), 4.4- 4.8 (8H, m, O*CH*$_2$Ph), 7.2- 7.4 (20H, m, Ar*H*). Mass spectrum: m/z 543 $(M+H)^+$ 565 $(M+Na)^+$.

Example 11 2,3,4,6-Tetra-*O*-benzyl-1,5-di-*O*-mesyl-D-galactitol



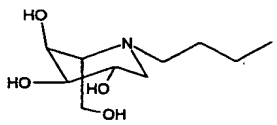
2,3,4,6-Tetra-*O*-benzyl-D-galactitol (7.6g) was stirred at 0°C in pyridine (20 ml) and a solution of mesyl chloride (2.5 ml) in pyridine (20 ml) was added. The solution was stored at 4°C overnight. TLC analysis showed completion of the reaction. The reaction mixture was partitioned between ethyl acetate and water/ice. The organic fractions were washed with 5% hydrochloric acid then saturated aqueous sodium bicarbonate solution, dried over Na_2SO_4 and concentrated to give a colourless oil which was used directly in the next stage (Example 12).

Example 12 Piperidine, 1-butyl-3,4,5-tris(phenylmethoxy)-2-[(phenylmethoxy)-methyl], (2S,3S,4R,5S)



The crude 2,3,4,6-tetra-*O*-benzyl-1,5-di-*O*-mesyl-D-galactitol (from Example 12) was dissolved in n-butylamine (50 ml) and stirred at 55°C for 5 days. The reaction mixture was concentrated and the crude oil purified by flash chromatography (gradient elution of 5 → 16% ethyl acetate/petroleum ether) to give piperidine, 1-butyl-3,4,5-tris(phenylmethoxy)-2-[(phenylmethoxy)-methyl], (2S,3S,4R,5S) (4.8g, 59% from 2,3,4,6-tetra-*O*-benzyl-1,5-di-*O*-mesyl-D-galactitol) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3H, J 6Hz), 1.25 (m, 2H), 1.4 (m, 2H), 2.6 (m, 3H), 2.8 (m, 1H), 3.0 (m, 1H), 3.4 (m, 1H), 3.55 (2H, m), 3.75 (1H, m), 3.8 (1H, m), 4.3- 4.6 (8H, m, O*CH*$_2$Ph), 7.15- 7.3 (20H, m, Ar*H*).

Example 13 3,4,5-Piperidinetriol, 1-butyl-2-hydroxymethyl)-, (2S,3S,4R,5S)



Piperidine, 1-butyl-3,4,5-tris(phenylmethoxy)-2-[(phenylmethoxy)-methyl], (2S,3S, 4R,5S) (4.8g) was dissolved in methanol (100ml) and stirred overnight under a hydrogen atmosphere in the presence of $PdCl_2$ (2.5g). TLC indicated completion of the reaction. The reaction mixture was filtered through celite (followed by a methanol/water wash) and concentrated to a 25ml aqueous solution. This solution

was slowly loaded onto 40ml of Amberlite IR-120(plus) resin which had been pre-washed with hydrochloric acid. The resin was washed with water then eluted with a mixture of 1:7 conc. aqueous ammonia:water (500ml). Product fractions were concentrated to give 3,4,5-piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2S,3S,4R,5S) (1.27g, 70%) as a colourless oil. ^{1}H NMR (D_2O): δ 0.95(3H, t), 1.35(m, 2H), 2.61(1H, dd), 2.70(1H, m), 2.87(1H, dd), 2.95(1H, ddd), 3.76(1H, ddd), 3.78(1H, dd), 3.90(1H, dd), 3.94(1H, ddd), 4.06(1H, dd).

Biological Data

The compounds of the invention were assayed (Table 1) to determine their IC_{50} concentrations against galactosidase and glucosylceramide synthase. In the former case, assays were carried out according to the methods described in Jacob and Scudder, *Methods in Enzymology* (1994), **230**, 280. In the case of glucosylceramide synthase, assays were carried out according to the method described in Platt *et al*, *J.Biol.Chem.* (1994), **269**, 27108. Both of these publications are herein incorporated by reference.

Table 1

Compound	Jack bean β-galactosidase (IC_{50} μM)	Mouse ceramide β-galactosidase (IC_{50} μM)	Porcine intestinal lactase (Ki μM)	Coffee bean α-galactosidase (IC_{50} μM)	Glucosyl ceramide synthase (IC_{50} μM)
NB-DGJ	3.4	370	85	12.6	32.5
Example 13	280	Not inhibitory	8000	72	73.1

Table 2 shows data for human enzymes. The assay for inhibition of GCS was performed essentially as described in Platt *et al*, *J.Biol.Chem.* (1994), **269**, 27108, the enzyme source being human recombinant GCS expressed in insect cells. The glucosidase assays were performed as described (Biochemical Genetics, A Laboratory Manual, Oxford University Press) except that *p*-nitrophenyl linked substrates were used instead of methylumbelliferone linked substrates.

Table 2

Compound	Human GCS	Human β-	Human α-	Human β-

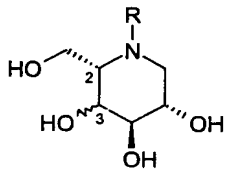
	(IC_{50} μM)	glucosidase (IC_{50} μM)	glucosidase (IC_{50} μM)	galactosidase (Ki μM)
NB-DNJ	15	960	<20 μM	No inhibition at 1mM
NB-DGJ		Not inhibitory	Not inhibitory	40
Example 7	10.6	Not inhibitory	Not inhibitory	Not inhibitory

Thus, the compounds of the invention exhibit less inhibitory action against both glucosidases and galactosidases (thereby reducing side effects) than compounds such as NB-DNJ or NB-DGJ, while retaining activity against glucosylceramide synthases.

5

CLAIMS:

1. A compound of formula I:



(I)

wherein

R is hydrogen, C_{1-16} straight or branched-chain alkyl, C_{1-10} alkylaryl where aryl is phenyl, pyridyl, thienyl or furyl wherein phenyl is optionally substituted by one or more substituents selected from F, Cl, Br, CF_3, OCF_3, OR^1, C_{1-6} straight or branched-chain alkyl; and

R^1 is hydrogen, C_{1-6} straight or branched-chain alkyl, and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1 which is:

3,4,5-Piperidinetriol, 1-propyl-2-(hydroxymethyl)-, (2S,3R,4R,5S);

3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2S,3R,4R,5S);

3,4,5-Piperidinetriol, 1-pentyl-2-(hydroxymethyl)-, (2S,3R,4R,5S);

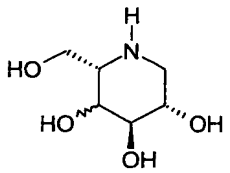
3,4,5-Piperidinetriol, 1-heptyl-2-(hydroxymethyl)-, (2S,3R,4R,5S); or

3,4,5-Piperidinetriol, 1-butyl-2-hydroxymethyl)-, (2S,3S,4R,5S).

3. A compound as claimed in claim 1 or claim 2 for use in medicine.

4. A process for the preparation of a compound as claimed in any one of claims 1 to 3 which comprises:

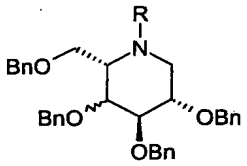
(a) reacting a compound of formula (II):



(II)

with $NaBH_3CN$ and an aldehyde of formula R^2CHO, wherein $R^2 = C_{1-15}$ straight or branched-chain alkyl, in acetic acid-methanol, or with $NaBH(OAc)_3$ and an aldehyde of formula R^2CHO, wherein $R^2 = C_{1-15}$ straight or branched-chain alkyl, in a solvent such as dichoromethane; or

(b) reacting a compound of formula (III):



Bn = CH_2Ph

(III)

wherein R is as defined in formula (I), in the presence of hydrogen gas and a catalyst such as $PdCl_2$ or palladium on carbon in a suitable solvent such as an alcohol, eg ethanol. It will be understood that when R = CH_2Ph this group can also be removed under these conditions to give compounds of formula (II).

5. A pharmaceutical formulation comprising at least one compound as defined in any one of claims 1 to 3 optionally together with one or more pharmaceutically acceptable carriers, excipients and/or diluents.

6. The use of a compound as defined in any one of claims 1 to 3 in the manufacture of an inhibitor of glucosylceramide synthase;

7. The use of a compound as defined in any one of claims 1 to3 in the manufacture of a medicament for the treatment of a glycolipid storage disease.

8. The use as claimed in claim 7 wherein the glycolipid storage disease is Gaucher disease, Sandhoffs disease, Tay-Sachs disease, Fabry disease or GM1 gangliosidosis.

9. The use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament for the treatment of Niemann-Pick disease types A and C.

10. The use of a compound s defined in any one of claims 1 to 3 in the manufacture of a medicament for the treatment of mucopolysaccharidosis type I, mucopolysaccharidosis type IIID, mucopolysaccharidosis type IIIA, mucopolysaccharidosis type VI and mucopolysaccharidosis type VII.

11. The use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament for the treatment of α-mannosidosis and mucolipidosis type IV.

12. The use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament for the treatment of neuronal cancer including neuroblastoma, brain cancer, renal adenocarcinoma, malignant melanoma, multiple myeloma and multi-drug resistant cancers.

13. The use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament for use in the treatment of Alzheimer's disease, epilepsy or stroke.

14. the use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament for use in the treatment of Parkinson's disease.

15. The use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament in the treatment of spinal injury.

16. The use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament for use in the treatment of disease caused by infectious microorganisms which utilize glycolipids on the surface of cells as receptors for the organism itself or toxins produced by the organism.

17. The use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament for use in the treatment of disease caused by infectious organisms for which the synthesis of glucosylceramide is an essential or important process.

18. The use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament for use in the treatment of diseases associated with abnormal glycolipid synthesis,eg polycystic kidney disease, diabetic renal hypertrophy and atherosclerosis.

19. The use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament for the treatment of a condition treatable by the administration of a ganglioside such as GM1 ganglioside.

20. The use as claimed in claim 19 wherein the condition is Parkinson's disease, stroke and spinal cord injuries.

21. The use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament for use in reversibly rendering a male mammal infertile.

22. A method for the treatment of a glycolipid storage disease, eg Gaucher's disease, Sandhoff's disease, Tay-Sachs disease or GM1 gangliosidosis, which comprises the step of administering to a patient an effective amount of a compound as defined in any one of claims 1 to 3.

23. A method for the treatment of Niemann-Pick disease, which comprises the step of administering to a patient an effective amount of a compound as defined in any one of claims 1 to 3.

24. A method for the treatment of mucopolysaccharidosis type I, mucopolysaccharidosis type IIID, mucopolysaccharidosis type IIIA, mucopolysaccharidosis type VI and mucopolysaccharidosis type VII which comprises the step of administering to a patient an effective amount of a compound as defined in any one of claims 1 to 3.

25. A method for the treatment of α-mannosidosis and mucolipidosis type IV which comprises the step of administering to a patient an effective amount of a compound as defined in any one of claims 1 to 3.

26. A method for the treatment of neuronal cancer including neuroblastoma, brain cancer, renal adenocarcinoma, malignant melanoma, multiple myeloma and multi-drug resistant cancers which comprises the step of administering to a patient an effective amount of a compound as defined in any one of claims 1 to 3.

27. A method for the treatment of disease caused by infectious microorganisms which utilize glycolipids on the surface of cells as receptors for the organism itself or toxins produced by the organism which comprises the step of administering to a patient an effective amount of a compound as defined in any one of claims 1 to 3.

28. A method for the treatment of disease caused by infectious organisms for which the synthesis of glucosylceramide is an essential or important process which comprises the step of administering to a patient an effective amount of a compound as defined in any one of claims 1 to 3.

29. A method for the treatment of diseases associated with abnormal glycolipid synthesis such as polycystic kidney disease, diabetic renal hypertrophy and atherosclerosis, which comprises the step of administering to a patient an effective amount of a compound as defined in any one of claims 1 to 3.

30. A method for the treatment of Alzheimer's disease, epilepsy, stroke or spinal injury which comprises the step of administering to a patient an effective amount of a compound as defined in any one of claims 1 to 3.

31. A method for the treatment of Parkinson's disease, which comprises the step of administering to a patient an effective amount of a compound as defined in any one of claims 1 to 3.

32. A method for reversibly rendering a male mammal infertile comprising the step of administering to said male mammal an effective amount of a compound as defined in any one of claims 1 to 3.

Figure 1

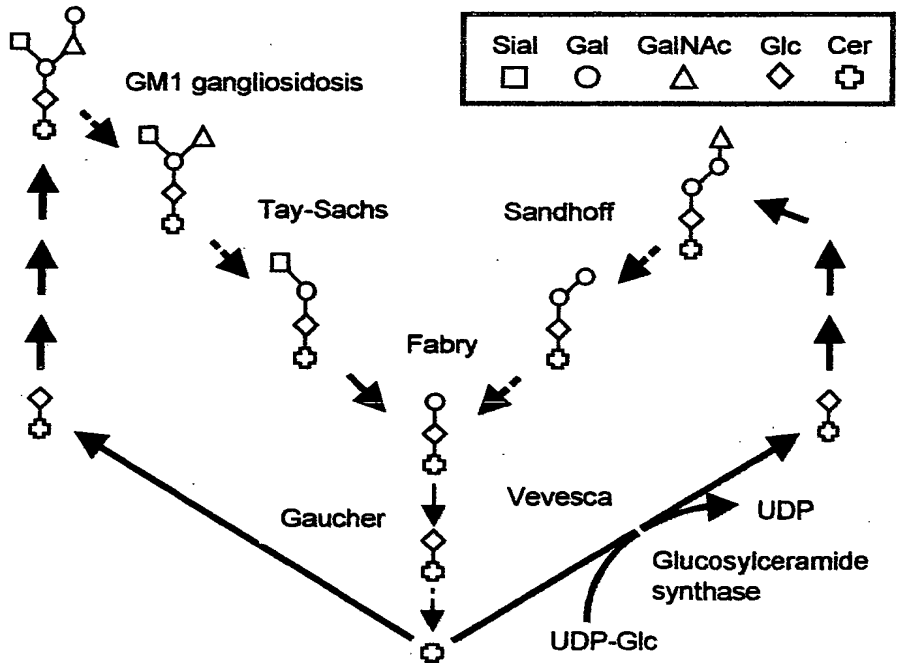
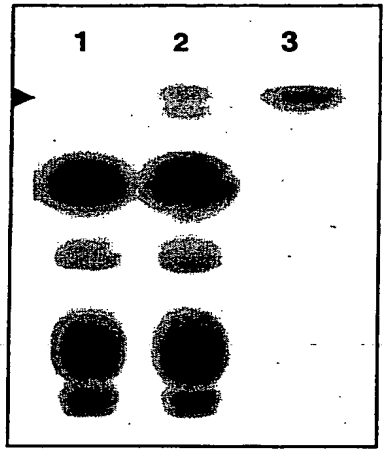

Sial
Gal
GalNAc
Glc
Cer
GM1 gangliosidosis
Tay-Sachs
Sandhoff
Fabry
Gaucher
Vevesca
UDP
Glucosylceramide synthase
UDP-Glc

Figure 2

2a



2b

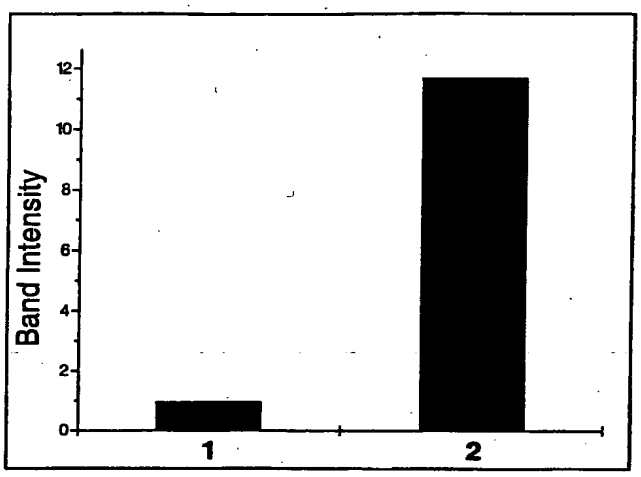


Figure 2a shows a thin layer chromatography (TLC) chromatogram of the non-polar lipid fraction extracted from MCF-7 breast carcinoma cells treated for 7 days with 50 μM OGT1655 (1), MCF-7 breast carcinoma cells (2), (3) represents a glucosylceramide standard.

Figure 2b represents a measure of the glucosylceramide band intensity from the TLC chromatogram relative to background. (1) represents the OGT1655 treated sample and (2) the untreated control.

Example 7